Validation of a procedure to mix homogenous solutions in bags and syringes

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ABSTRACT

Objectives It is essential to obtain homogeneous drug mixtures, especially when only a fraction of the prepared dose is to be administered. This study aimed to validate a manual mixing method for guaranteeing homogeneity.

Methods One operator tested six standardised manual mixing techniques (one, five and 10 inversions, and one, five and 10 bottoms-up agitations) six times each for preparations in bags and syringes. The mixing step was reproduced experimentally by adding a small volume of analyte (0.8 mL for syringes and 6 mL for bags) to a large volume of matrix (50 mL for syringes and 300 mL for bags). Three analyte/matrix pairings were tested: water/water, water/glucose 20% and glucose 20%/water. The tracer (sodium chloride) was assayed using capillary electrophoresis. Volume measurement errors were corrected by weighing bags and syringes. In order to evaluate inter-individual variability, the 10 inversions technique was tested by 10 drug preparation technicians. Mixtures were considered acceptable if they were between 95% and 105% accurate and if the coefficient of variation was $\leq 5\%$ of the average of the six repetitions.

Results Both the 10 inversions and 10 bottoms-up agitations mixing techniques ensured acceptable mixtures by the principal technician in all tested conditions. When mixing using the 10 inversions method was tested by the 10 technicians, the mixture's mean acceptability could no longer be ensured.

Conclusion Use of a standardised mixing technique did not appear to be sufficient to obtain a homogeneous mixture across technicians. Standardised guidelines for needle position, needle rinsing and speed of addition should be implemented.

INTRODUCTION

Drug mixing is a complex operation involving hydrodynamic, thermal, chemical and mechanical factors. It is key to obtaining the homogeneous solutions which are essential for safe drug preparation, both in the pharmacy by drug preparation technicians and on wards by nurses.

According to the WHO's Good Manufacturing Practices (GMP),¹ the mixing procedure must be detailed in the manufacturer's instructions so as to ensure the quality, reproducibility and uniformity of the solutions prepared. Homogeneous solutions are particularly important when only a fraction of the prepared dose is to be administered. For example, during the preparation of a batch of solution for the intravenous injection of midazolam, adjusting the solution to pH 3 requires the addition of a hydrochloric acid solution. A very low volume of this

acid solution (a few drops) must be added to a large volume of midazolam solution (several thousand millilitres). A heterogeneous initial mixture would result in pH variability between bags in the same batch and would affect the preparation's stability. Another example would be the preparation of a batch of ready-to-use syringes from a stock solution prepared in a bag or another large syringe. This stock solution must be diluted and mixed before being divided into several small-volume syringes. A heterogeneous initial mixture could result in variability in the concentration of the active ingredient in syringes of the same batch.

Obtaining a homogeneous drug mixture is also essential because not every sample from a batch of prepared units can undergo quality control, so checked units must accurately reflect the concentration of the whole batch. An initially heterogeneous drug mixture could result in a concentration outside the specified limits in one of the samples and to rejection of the entire batch.

On wards, nurses mix drug solutions extemporaneously and there is no quality control. In some cases, heterogeneous drug mixtures could pose a risk. For example, in neonatal and paediatric intensive care units, nurses often prepare double the necessary dose of a drug in order to flush lines with the excess and ensure that they administer the correct dose. This practice is common, and drugs are regularly mixed with high concentrations of glucose (10%–40%) in order to decrease the volume administered and ensure a sufficient intake of carbohydrates. Obtaining homogeneity in these viscous solutions is more difficult than in aqueous media such as 0.9% sodium chloride solution. Without a validated mixing procedure, heterogeneous solutions might be inadvertently administered to patients.

Heterogeneous mixtures of certain drugs, such as electrolytes, cyclosporine, antibiotics and several anticancer agents, also increase the risk of toxicity.² This especially concerns drugs that must be administered at low infusion rates. For example, in intensive care units, administration of a heterogeneous preparation of potassium chloride could have life-threatening consequences. Similarly, a heterogeneous solution of insulin could complicate the management of glycaemia.

Very few studies to date have investigated the mixing step.^{2–6} Some have shown that in the absence of standardised procedures, mixing in bags is often incomplete.^{3–5–7} To the best of our knowledge, no study has clearly evaluated the mixing of solutions in syringes or the impact of viscous diluents such as glucose 20%, despite the fact that they are used in daily practice.

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Figure 1 Inversion.

Furthermore, in cases involving manual drug mixing, there could be inter-individual variability depending on the technique employed or the duration of mixing, and this has never been clearly evaluated. The various routinely used mixing techniques (inversions, bottoms-up agitations and rotations) have not been tested regarding the homogeneity of the mixtures in bags and syringes.

The present study examined the homogeneity of mixtures, in syringes and bags, of solutions in aqueous (water) and viscous (glucose 20%) diluents, after different standardised mixing procedures had been applied. Inter-individual variability during the mixing stage was also examined.

METHODS

Validation of a standardised procedure

The same drug preparation technician tested two standardised mixing procedures on bags and syringes: inversions ([figure 1](#)) and bottoms-up agitations ([figure 2](#)). The mixing step was reproduced experimentally by adding a small volume of analyte (0.8 mL for syringes; 6 mL for bags) to a large volume of matrix (50 mL for syringes; 300 mL for bags). The analytes were either an aqueous (water) or viscous (glucose 20%) solution of sodium chloride 5 M for preparations in syringes and either an aqueous (water) or viscous (glucose 20%) solution of sodium chloride 4 M for preparations in bags. The matrix was either an aqueous (water) or viscous solution (glucose 20%). Three analyte/matrix pairs were tested: water/water, water/glucose 20% and glucose 20%/water. In order to correct measurement errors for the volumes of analyte and matrix used, bags and syringes were weighed on a calibrated scale both before and after the addition of each solution, and the solution densities were measured using a density meter. Dead volumes were also determined by weighing syringes before and after the analytical solution was added to the matrix.

Six mixing techniques (one, five and 10 inversions, and one, five and 10 bottoms-up agitations) were each tested six times on bags and six times on syringes. During the addition of the analyte, syringes and bags were held vertically. After mixing, 0.5 mL samples were directly collected at the entry port of bags or at the tip of syringes, which were equipped with an 18 gauge needle.

Figure 2 Bottoms-up agitation.

Sodium chloride was assayed using a validated capillary electrophoresis method.⁸ Each result was the mean of two replicate analyses and was considered the mixture's true concentration.

Using the hypothesis that the mixture was homogeneous, a theoretical final mixture concentration was calculated by taking into account the dead volume and the exact volumes of the matrix and the analyte. Accuracy was expressed as a percentage and calculated as follows: $\text{accuracy} = (\text{real concentration} / \text{theoretical concentration}) \times 100$. A coefficient of variation was also calculated by using the average of the six repetitions for each mixture.

Inter-individual variability

Ten drug preparation technicians were selected to use the analyte/matrix pairing of water/glucose 20% to test the standardised 10 inversions technique on bags and on syringes, six times each per container.

In both parts of the study, the mixture was considered acceptable if accuracy was between 95% and 105% and if the average coefficient of variation (CV) was $\leq 5\%$ over the six repetitions.

RESULTS

Validation of a standardised procedure

The accuracy and CV of mixtures in syringes according to the various analyte/matrix pairs are presented in [figure 3](#). The accuracy and CV of mixtures in bags according to the various analyte/matrix pairs are given in [figure 4](#).

Inter-individual variability

The accuracy and CV of mixtures obtained for bags and syringes following 10 inversions by 10 drug preparation technicians are given in [figure 5](#).

For bags, participant no. 7 had to be excluded due to mishandling during the experiment. Indeed, he switched bags and they could thus not be weighed before and after addition of the matrix to calculate their exact volume, the theoretical final concentration and accuracy (%).

Figure 3 Accuracy (%) and coefficients of variation of mixtures in syringes.

DISCUSSION

The first part of this study demonstrated that the 10 inversions and the 10 bottoms-up agitations mixing techniques both ensured acceptable mixtures in syringes in aqueous and viscous solutions. Fewer agitations or inversions were associated with solutions which failed to fulfil our specifications: they had $CV > 5\%$ and accuracy below 95% and thus were not considered homogeneous.

The five inversions, 10 inversions and 10 bottoms-up agitations mixing techniques all ensured acceptable mixtures in bags with both aqueous and viscous solutions. The other mixing techniques failed to produce acceptable homogeneity. These results complement those obtained by Deardorff *et al.*⁷ Indeed, by adding 20 mL of potassium chloride solution to 1000 mL bags of intravenous fluids, they demonstrated that two inversions were insufficient and four inversions were recommended to ensure homogeneity of the mixture.

We also noticed that for certain mixing techniques, the homogeneity of the solutions in bags and syringes varied significantly depending on the viscosity of the solution. Thus

Figure 4 Accuracy (%) and coefficients of variation of mixtures in bags.

Figure 5 Accuracy (%) and coefficients of variation of mixtures obtained using 10 inversions, as tested by 10 drug preparation technicians for bags and syringes for the analyte/matrix pairing of water/glucose 20%.

during the validation of a mixing technique, it is essential to estimate the homogeneity of solutions in both aqueous and viscous media.

In the second part of the study, the 10 inversions mixing technique did not result in homogeneous mixtures for all the drug preparation technicians. Three out of nine participants failed to prepare acceptable mixtures in bags, and three out of 10 failed to prepare acceptable mixtures for syringes. This result was surprising because the 10 inversions mixing technique had been validated by a single technician to ensure homogeneous mixtures under all test conditions. The addition step, before mixing, may explain the observed inter-individual variability. It seems that homogeneity can vary according to the position of the bag, the position of the needle, how effectively the needle is rinsed and the time taken for addition. This variability in the addition stage was also noticed by Deardorff *et al.*³ Indeed, they carried out an experiment to study how the different parameters of the addition step affected the homogeneity of solutions. To do this, they added 15 mL of potassium chloride solution to 1000 mL infusion bags and varied the different parameters without mixing bags. They calculated the percentage of mixtures according to the bag position (vertical or horizontal), the needle position (parallel or perpendicular to the bag) and the time needed for addition (10,

Key messages

What is already known on this subject

- ▶ Very few studies to date have investigated the mixing step when preparing drug mixtures.
- ▶ Some have shown that in the absence of standardised procedures, mixing in bags is often incomplete.

What this study adds

- ▶ Ten inversions or 10 bottoms-up agitations were required to obtain homogeneous solutions in bags and syringes, both with aqueous and viscous media.
- ▶ Simply using a standardised manual mixing technique does not appear to be sufficient to obtain a homogeneous drug mixture.
- ▶ The addition step, before mixing, was also subject to significant inter-individual variability.

20 and 30 s). They also showed that in order to obtain the best mixture it was necessary to hold the bag in a horizontal position, to hold the needle parallel to the bag and to inject the analyte quickly (within 10 s). In the present study, the drug preparation technicians had to maintain the needles, bags and syringes in a constant vertical position, but they had no constraints on the time taken for addition and needle rinsing. These two parameters partially explained the inter-individual variability observed during our experiments.

CONCLUSION

The present study complements the results obtained by Deardorff *et al*³ and allows us to propose a standard mixing procedure that could be used routinely for pharmacy preparations. In order to have the best mixture in an aqueous or viscous medium, it is necessary to hold the bag or the syringe in a horizontal position, to hold the needle parallel to the bag or the syringe, to inject the analyte quickly (within 10 s) and to mix with the standardised 10 inversions mixing technique or the 10 bottoms-up agitations mixing technique.

Competing interests None declared.

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